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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,385	07/06/2001	Joyce A. Deleo	DC-0156	4729

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	**PAPER NUMBER**
1614	

NOTIFICATION DATE	DELIVERY MODE
01/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	09/857,385	DELEO ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments filed September 19, 2007 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, "into the spinal cord but not the brain" (present claim 1) is a concept that was not present in the specification as originally filed.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. The administration of methotrexate intrathecally "into the spinal cord but not the brain" is not specifically recited in the instant specification. Regarding applicants' assertion that the Anatomy and Physiology text,

Human Anatomy and Physiology, second edition, pages 404-405 teach that the circulation of the cerebrospinal fluid through the brain ventricles is designed such that only a very small amount of the CSF from the ventricles circulates into the central canal of the spinal cord, this lacks written basis as filed for such a limitation, because the text, Human Anatomy and Physiology, has neither been incorporated by reference in the instant application, nor has the brain administration negative limitation been disclosed as instantly filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (Archives of Neurology) and Biomethodology of the Rat (U).

Chamberlain et al. teach administration of methotrexate to patients with leptomeningeal metastases presenting with radiculopathy (see abstract). Methotrexate is administered intraventricularly in doses of 2 mg daily (total dose of 40 mg) (see page 508, column 1). Chamberlain et al. teach the same composition of methotrexate in the same dose to be useful in treatment of leptomeningeal metastases with radiculopathy. The prior art differs in that it does not teach intrathecal administration into the spinal cord. However Chamberlain et al. teach intraventricular administration. The definition of intrathecal administration from Stedman's Medical Dictionary, 27th edition is administration within either the subarachnoid or the subdural space. Since the method of administering an agent intrathecally can mean that the agent is administered into the subarachnoid or subdural space, the method of administering intrathecally overlaps with Chamberlain's method of administering intraventricularly to treat leptomeningeal metastases with radiculopathy. Applicant has added the limitation that the injection site is intrathecally into the spinal cord but not the brain. However, there does not appear to be a basis for this exclusionary proviso in the instant case (see above). Regarding the

location of the injection, an intrathecal injection of the instant claims is obvious over the intraventricular injection of the prior art. Applicant's reference provided on May 11, 2006 teaches that "once produced, cerebrospinal fluid (CSF) moves freely through the ventricules. Some CSF circulates from the ventricles into the central canal of the spinal cord. Although the prior art administers methotrexate for treatment of leptomeningeal metastasis, it provides relief of the symptoms, such as radiculopathy, and as such, it is reasonable and self-evident that methotrexate must treat the radiculopathy in each case, whether explicitly recognized or not. It would have been made obvious to one of ordinary skill in art at the time it was made to administer methotrexate in a dose of 1 mg/kg and not greater than 2 mg/kg each day to reduce lower back pain with radiculopathy motivated by the teaching of Chamberlain et al. who teaches that methotrexate is effective at a dose of 2 mg administered intraventricularly to treat leptomeningeal metastasis with radiculopathy. Chamberlain administers 2 mg/day methotrexate to a human patient who has leptomeningeal metastasis with radiculopathy, and the radiculopathy is resolved. The instant claims are drawn to an animal. When one looks that the specification for clarification of the animal, page 7 of the instant specification identifies the animal as a rat. The claim states that dosages of 1 mg/kg are to be administered, but does not state the frequency of the administration. In Biomethodology of the Rat (U) the weight of a laboratory rat is from about 250 grams to about 800 grams. To convert this weight to a dose that fits the claim, an 800 gram rat would receive 0.8 mg of methotrexate. Chamberlain administers 2 mg/day. As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and

serve as useful guideposts for the physician. There are, however, many reasons for varying dosages. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. For these and other self-evident reasons, it would have been obvious to have used methotrexate in a dosage of 1 mg/kg.

Response to Arguments

Regarding the administration step of "intrathecally into the spinal cord but not the brain", Applicant states that this is from knowledge of one skilled in the art at the time the application was filed and states the MPED 2163 as the authority in that "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. In response, Applicant's reference provided on May 11, 2006 teaches that "once produced, cerebrospinal fluid (CSF) moves freely through the ventricules. Some CSF circulates from the ventricles into the central canal of the spinal cord. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. The intraventricular dose of methotrexate of Chamberlain et al. circulates into the spinal cord, thus the intraventricular administration of methotrexate of the instant claims does not patentably distinguish over the intraventricular dose of Chamberlain et al. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the concentration of MTX in the spinal cord) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification,

limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding the dosage, Chamberlain et al. administers 2 mg/day methotrexate to a human patient who has leptomeningeal metastasis with radiculopathy, and the radiculopathy is resolved. The instant claims are drawn to an animal. When one looks that the specification for clarification of the animal, page 7 of the instant specification identifies the animal as a rat. The claim states that dosages of 1 mg/kg are to be administered. Chamberlain administers 2 mg/day. One of ordinary skill in the art would understand that depending on the malady, methotrexate is dosed in mg/m2 or it is dosed empirically, in 1 or 2 mg doses. In Chamberlain et al., the methotrexate is dosed empirically, at 2mg /day dosed intraventicularly. The dosing of methotrexate would vary depending upon the malady being treated, the method of administration, the salt of the drug, and co-administration with other agents, such as leucovorin.

Jones et al. teach that Methotrexate is a toxic medication, but if it is dosed correctly and monitored appropriately, its toxic effects can be minimized. These effects are categorized as minor or major. Major toxic effects of methotrexate may be life threatening (page 2). Methotrexate should never be given in daily doses. More frequent administration than weekly increases the risk of toxicity. Most patients show a therapeutic response with weekly doses of oral or injection therapy between 7.5 mg and 15.0 mg, although some patients may need 20 or even 30 mg, the maximum recommended dose (pages 5-6). Note that methotrexate is not administered on a mg/kg basis because of the risk of death. It is dosed in mg/m2 or in an empiric dose

depending on the malady being treated. In the instant case, if the animal being treated was a human, the dose of 1mg/kg for an 80 kg human (80 mg) would be toxic unless leucovorin rescue was performed. Thus Applicants' arguments drawn to dosing of methotrexate by one of skill in the art is incorrect.

Applicant asserts that Chamberlain et al. disclose only use of a 2 mg dose of methotrexate intraventricularly in humans to treat a form of metastatic cancer and nowhere in this reference is it suggested or taught that the 2mg dose could be modified and given to any other species on the basis of mg drug per kg body weight. In response, although the prior art administers methotrexate for treatment of leptomeningeal metastasis, it provides relief of the symptoms, such as radiculopathy, and as such, it is reasonable and self-evident that methotrexate must treat the radiculopathy in each case, whether explicitly recognized or not. Applicant asserts that the claims distinguish because the method of treatment is drawn to "an animal" not a "human". In response, the genus "animal" does not exclude humans.

Regarding the assertion that the dosing of methotrexate is different for pain vs. treatment of cancer, in response, a dose of 1mg/kg in a human animal would be no less toxic whether it is administered for pain or cancer, unless a leucovorin rescue is initiated within 12 hours of administration of the methotrexate.

Regarding the teaching in the instant specification regarding a defining dosage across different species, it is well established that the specification teaches an invention, whereas the claims define the **right to exclude**. *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 [227 USPQ 577] n.14 (Fed. Cir. 1985).

The prior art teaches administration of methotrexate in doses of 2 mg via intraventricular administration whereby radiculopathy is resolved.

One of ordinary skill in the art would be motivated to administer 1mg/kg vs. 2mg motivated by the knowledge of one of ordinary skill in the art, such as a physician, that the preferred dosages are merely exemplary and serve as useful guideposts. There are, however, many reasons for varying dosages. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity or the use of a folate or leucovorin.

One of ordinary skill in the art, in view of the known toxicities of methotrexate in the human animal would be motivated to adjust the dosage accordingly and thereby gain, predictably, the benefit of the treatment of radiculopathy.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Patent Examiner

Art Unit 1614

January 18, 2008

Ardin H Marschel 1/22/08

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER